Journal of the American College of Cardiology Vol. 50, No. 9, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.04.075

Metabolic Syndrome Increases Operative Mortality in Patients Undergoing Coronary Artery Bypass Grafting Surgery

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Objectives The aim of this study was to determine the impact of the metabolic syndrome (MS) on operative mortality after a coronary artery bypass grafting surgery (CABG).

Background Diabetes and obesity are highly prevalent among patients undergoing CABG. However, it remains unclear whether these factors have a significant impact on operative mortality after this procedure. We hypothesized that the metabolic abnormalities associated with MS could negatively influence the operative outcome of CABG surgery.

Methods We retrospectively analyzed the data of 5,304 consecutive patients who underwent an isolated CABG procedure between 2000 and 2004. Of these 5,304 patients, 2,411 (46%) patients met the National Cholesterol Education Program–Adult Treatment Panel III criteria for MS. The primary end point was operative mortality.

Results The operative mortality after CABG surgery was 2.4% in patients with MS and 0.9% in patients without MS ($p < 0.0001$). The MS was a strong independent predictor of operative mortality (relative risk 3.04 [95% confidence interval (CI) 1.73 to 5.32], $p = 0.0001$). After adjusting for other risk factors, the risk of mortality was increased 2.69-fold (95% CI 1.43 to 5.06; $p = 0.002$) in patients with MS and diabetes and 2.36-fold (95% CI 1.26 to 4.41; $p = 0.007$) in patients with MS and no diabetes, whereas it was not significantly increased in the patients with diabetes and no MS.

Conclusions This is the first study to report that MS is a highly prevalent and powerful risk factor for operative mortality in patients undergoing a CABG surgery. Thus, interventions that could contribute to reduce the prevalence of MS in patients with coronary artery disease or that could acutely modify the metabolic perturbations of MS at the time of CABG might substantially improve survival in these patients. (J Am Coll Cardiol 2007;50:843–51) © 2007 by the American College of Cardiology Foundation

Diabetes and obesity are highly prevalent in the population undergoing coronary artery bypass grafting (CABG). These risk factors have been shown to have a significant impact on morbidity after CABG (1–9). Metabolic syndrome (MS) is a cluster of metabolic perturbations largely resulting from the presence of abdominal obesity, which is associated with an increased risk of type 2 diabetes and cardiovascular disease (10,11).

The MS largely results from the accumulation of abdominal fat and is characterized by insulin resistance, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and a pro-inflammatory and pro-thrombotic state (12). The prevalence of MS has been estimated to reach approximately 35% to 40% of the population of industrialized countries (13). We hypothesized that the pro-inflammatory and pro-thrombotic features of MS could adversely affect the operative outcome in patients undergoing the CABG procedure. The objective of this retrospective study was thus to determine the impact of MS on operative mortality after a CABG surgery.

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Manuscript received December 8, 2006; revised manuscript received April 12, 2007, accepted April 24, 2007.

JACC Vol. 50, No. 9, 2007
August 28, 2007:843–51

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
HDL = high-density lipoprotein
LDL = low-density lipoprotein
MI = myocardial infarction
MS = metabolic syndrome
RR = relative risk

Methods

Patient population. The preoperative and operative data of all patients undergoing a cardiac surgery in our institution were prospectively collected and entered in a computerized database. Postoperative complications were also recorded prospectively by trained personnel composed of a research nurse and a medical archivist. All major adverse events were prospectively validated by an experienced cardiac surgeon according to standard definitions. A fasting plasma lipid profile (including total cholesterol, low-density lipoprotein [LDL] cholesterol, HDL cholesterol, and triglyceride levels) and blood pressure were also assessed in the resting state. Furthermore, waist circumference was systematically measured since January 2000. For this study, we included patients who underwent a first CABG operation without associated procedures between January 2000 and December 2004. During this period, 5,829 patients underwent a first CABG procedure, and from this group the data concerning MS status were available for 5,304 patients, which constitute the population of this study. The missing data regarding the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) criteria for the 525 patients not included in the present analyses were, in part, explained by the fact that a large proportion (53%) of these patients underwent operation on an emergency basis, thus allowing less time before surgery to acquire the relevant information.

Operative technique. During the study period, a team of 12 surgeons performed the CABG procedures. Anesthetic and surgical techniques were standardized for all patients. Patients were operated through a mid-sternotomy. In patients operated with cardiopulmonary bypass (93.7% of the total patients), moderate systemic hypothermia (32°C) and intermittent antegrade cold blood cardioplegia were used. Proximal anastomoses were performed routinely on a side biting clamp. In patients operated off-pump (6.3%), coronary stabilization was obtained with a pressure type stabilizer doing the distal anastomoses first (14). After surgery, patients were transferred to the intensive care unit. They were extubated as soon as they met the following criteria: normothermia, consciousness, hemodynamic stability, and no significant bleeding.

Clinical and laboratory data. Clinical data included history of smoking and documented diagnoses of hypertension (patients receiving antihypertensive medications or having known but untreated elevated blood pressure [≥130/85 mm Hg]), diabetes (patients with established diagnoses currently receiving oral hypoglycemic medication or insulin), obesity (body mass index ≥30 kg/m^2), and renal failure (creatinine >150 μmol/l).

Identification of patients with MS. The clinical identification of patients with the features of MS was based on the modified criteria proposed by the NCEP-ATPIII (15). Patients were considered to have MS when 3 of the 5 following criteria were present: 1) waist circumference >102 cm in men and >88 cm in women; 2) fasting glycemia ≥6.1 mmol/l; 3) triglycerides ≥1.69 mmol/l; 4) HDL cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women; and 5) hypertension.

End points of the study. The primary end point was operative mortality defined as death from any cause within 30 days after operation or any interval if the patient was not discharged. The secondary end point was morbidity occurring during the hospital stay period. Perioperative myocardial infarction (MI) was defined as the appearance of a new Q-wave on the electrocardiogram or a rise in the creatine kinase-myocardial band (CK-MB) level ≥75 μg/l during the hospital stay period. The CK-MB levels were monitored during the first 48 h after surgery, whereas electrocardiograms were examined daily. A postoperative stroke was identified when a new central neurologic deficit was detected and lasted for more than 24 h or detected with imaging techniques when the patient died within the 24-h period after operation. The criterion for postoperative renal failure was an increase of at least 50% of the baseline serum creatinine level. The criterion for postoperative septicemia was the presence of a positive blood culture. A mediastinitis was diagnosed when a deep sternal infection was present, necessitating an opening of the wound with excision of tissue and treatment with antibiotics. The criteria for pneumonia included a positive culture of the sputum associated with a radiological infiltration.

Statistical analysis. Continuous variables were expressed as mean ± SD, whereas categorical data were expressed as percentages. For continuous variables, values were compared by using 2-sample *t* tests for independent samples. Differences in proportion were compared with a chi-square test or Fisher exact test, as appropriate. The association between operative mortality and the different risk factors was first examined by calculating relative risks (RRs) with age-adjusted univariate logistic analysis. A stepwise logistic regression was then used to develop a multivariate model that identified the best set of predictors of operative mortality. The multivariate models were constructed from the Hosmer-Lemeshow approach. The variables listed in Table 1 were first tested on univariate analysis, and those with a p value ≤0.25 were entered in the multivariate analyses. Backward analyses allowed elimination of the less significant variables. To detect a possible provider effect, the 12 surgeons who had performed the surgeries were entered as a covariable into the multivariate model.

To eliminate covariate differences that might lead to biased estimates of MS effect, a propensity score adjust-

Table 1 Preoperative and Operative Data of Patients Undergoing CABG, With and Without Metabolic Syndrome

	All Patients (n = 5,304)	Metabolic Syndrome		p Value
		Absent (n = 2,893)	Present (n = 2,411)	
Age, yrs	64 ± 10	64 ± 10	65 ± 10	0.39
Female patients	23.3%	16.1%	31.9%	<0.0001
Body mass index, kg/m^2	28 ± 5	26 ± 4	30 ± 5	<0.0001
Waist circumference, cm	100 ± 13	96 ± 11	106 ± 12	<0.0001
Risk factors and concomitant diseases				
Underweight (<18.5 kg/m^2)	0.7%	1.1%	0.3%	0.0002
Normal weight (18.5–24.9 kg/m^2)	26.1%	37.1%	12.9%	<0.0001
Overweight (25.0–29.9 kg/m^2)	44.5%	47.9%	40.4%	<0.0001
Obesity (≥30 kg/m^2)	28.7%	13.9%	46.5%	<0.0001
Active smokers	18.7%	19.5%	17.8%	0.11
Hypertension	64.3%	47.0%	85.1%	<0.0001
Diabetes mellitus	31.4%	16.6%	49.0%	<0.0001
HDL cholesterol, mmol/l	1.12 ± 0.32	1.21 ± 0.32	1.00 ± 0.27	<0.0001
LDL cholesterol, mmol/l	2.31 ± 0.87	2.33 ± 0.84	2.29 ± 0.90	0.09
Triglycerides, mmol/l	1.67 ± 1.01	1.30 ± 0.61	2.11 ± 1.20	<0.0001
Fasting glycemia, mmol/l	6.16 ± 2.04	5.54 ± 1.32	6.91 ± 2.45	<0.0001
Microalbuminuria ≥20 mg/l	29.5%	21.3%	33.5%	<0.0001
Parsonnet score >20	8.1%	5.0%	11.8%	<0.0001
Functional CCS class IV*	17.3%	16.7%	18.0%	0.24
Peripheral vascular disease	15.6%	13.6%	18.0%	<0.0001
COPD	10.7%	10.3%	11.2%	0.28
Renal failure (creatinine >150 μmol/l)	6.2%	4.4%	8.4%	<0.0001
Left ventricular ejection fraction <40%	8.0%	8.0%	7.9%	0.91
Left main stenosis ≥50%	47.1%	48.1%	45.9%	0.31
2-vessel disease	37.1%	36.9%	37.4%	0.68
3-vessel disease	50.1%	49.0%	51.4%	0.08
Previous cardiovascular events				
MI	49.0%	49.2%	48.9%	0.85
MI within 7 days before surgery	7.2%	7.7%	6.7%	0.38
Stroke	4.8%	4.3%	5.5%	0.038
Atrial fibrillation	4.1%	4.4%	3.8%	0.23
Previous coronary artery dilation/stenting	12.4%	12.2%	12.8%	0.52
Operative data				
Operative status				
Elective	70.1%	70.3%	70.0%	0.85
Urgent	29.3%	29.2%	29.4%	0.87
Emergent	0.6%	0.6%	0.6%	0.89
Cardiopulmonary bypass time (min)	75 ± 23	74 ± 23	76 ± 23	0.0007
Aortic cross-clamp time (min)	49 ± 18	48 ± 17	50 ± 18	0.005
Volume of cardioplegia (ml/min AoX)	40 ± 19	39 ± 12	41 ± 25	0.20
Mammary artery graft	92.8%	92.1%	91.4%	0.38
Off-pump bypass surgery	6.3%	6.2%	6.4%	0.68
Operative mortality	1.6%	0.9%	2.4%	<0.0001

Mean ± SD for continuous variables are shown. *Functional class for angina as defined by the Canadian Cardiovascular Society (CCS).

AoX = aortic cross-clamp time; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

ment was also used (16). Propensity score was computed with logistic regression with the dependent variable being MS and the independent variables (covariates) being gender, peripheral vascular disease, chronic obstructive pulmonary disease, preoperative renal failure, preoperative MI, and preoperative stroke. We estimated the adjusted relative operative mortality risk associated with MS by using the propensity score as a covariate into the model. Propensity-based matching with a conditional logistic model was also used to select control patients who are similar to patients with MS with respect to propensity score and other covariates such as age, discarding unmatched individuals. A p value <0.05 was considered significant. All the statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina).

Table 2 Prevalence and Distribution of the NCEP-ATPIII Criteria for Metabolic Syndrome in Patients With and Without Metabolic Syndrome

	All Patients (n = 5,304)	Metabolic Syndrome		p Value
		Absent (n = 2,893)	Present (n = 2,411)	
Waist circumference >102 cm in men and >88 cm in women	49.2%	24.0%	79.1%	<0.0001
Fasting glycemia ≥6.1 mmol/l	34.9%	16.1%	57.5%	<0.0001
Triglycerides ≥1.69 mmol/l	37.4%	14.3%	65.3%	<0.0001
HDL cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women	52.3%	30.4%	78.6%	<0.0001
Hypertension	64.3%	47.0%	85.1%	<0.0001
0 criteria	431 (8.1%)	431 (14.9%)	0	
1 criteria	1,208 (22.8%)	1,208 (41.8%)	0	
2 criteria	1,254 (23.6%)	1,254 (43.3%)	0	
3 criteria	1,369 (25.8%)	0	1,369 (56.8%)	
4 criteria	783 (14.8%)	0	783 (32.5%)	
5 criteria	259 (4.9%)	0	259 (10.7%)	

HDL = high-density lipoprotein; NCEP-ATPIII = National Cholesterol Education Program–Adult Treatment Panel III.

Results

Patient characteristics. During the study period, a total of 5,304 patients for whom MS status was known underwent a first isolated CABG procedure. Of those patients 2,411 (46%) patients met the criteria for MS. The baseline characteristics for the different groups are presented in Table 1, and the distribution of the NCEP-ATPIII criteria used to define MS is presented in Table 2. When compared with patients without MS, those with MS had a higher proportion of women, a higher prevalence of hypertension, diabetes, obesity, peripheral vascular disease, renal failure, and a previous history of stroke (Table 1). In addition patients with MS had, as expected, higher fasting glycemia, higher plasma triglyceride levels, lower HDL cholesterol concentrations, and a higher prevalence of microalbuminuria. The proportion of patients with a Parsonnet score >20, evaluating the operative risk, was significantly higher in patients with MS. The average volume of cardioplegia received per minute of aortic cross-clamp time was similar in both groups.

Mortality and morbidity. Overall, operative mortality was 1.6%, studying the entire cohort of patients included in this study. The operative mortality was markedly higher ($p < 0.0001$) in patients having MS (2.4%) than in those without MS (0.9%) (Table 1). When adjusted for age, MS was associated with a 2.8-fold increase in the risk of mortality (Table 3). There was no cumulative effect with respect to the number of NCEP-ATPIII components of MS (Fig. 1). Among the other risk factors, age >75 years, female gender, being underweight (body mass index <18.5 kg/m^2), hypertension, fasting glycemia ≥6.1 mmol/l, peripheral vascular disease, chronic obstructive pulmonary disease, renal failure, left ventricular ejection fraction <40%, history of MI within 7 days before surgery, stroke, urgent or emergent operative status, and cardiopulmonary bypass time >120 min were significantly associated with higher operative mortality (Table 3). The stratification of the analysis according to gender revealed that the impact of MS on mortality was comparable between men (2.60 [95% confidence interval (CI) 1.44 to 4.70] [$p = 0.0015$]) and women (2.39 [95% CI 1.03 to 5.54] [$p = 0.04$]).

On multivariate analysis, MS was independently associated with increased operative mortality with an RR of 3.04 (95% CI 1.73 to 5.32 [$p = 0.0001$]) (model #1, Table 4). The other independent risk factors for mortality were: age >75 (RR 2.72), being underweight (RR 11.07), preoperative renal failure (RR 2.44), cardiopulmonary bypass time >120 min (RR 5.65), and urgent/emergent operative status (RR 2.18 and 5.54, respectively). The surgeon variable was not independently associated with increased mortality, which further supports the adequacy of the standardization of surgical technique among the different surgeons who performed CABG procedures. Diabetes, hypertension, obesity, as well as the 5 components of MS included in the definition of the NCEP-ATPIII were not independently associated with increased operative mortality. When the 5 components of MS (included as dichotomous variables) and MS were entered in a sequential manner in a multivariate model (model #2) including other covariates, MS remained independently associated with operative mortality: RR 4.06 (95% CI 1.51 to 10.9; $p = 0.005$). When entering MS components as continuous variables instead of dichotomous, MS remained independently associated with operative mortality: RR 2.8 (95% CI 1.31 to 5.97; $p = 0.008$).

The MS was associated with higher mortality rates in both nondiabetic (2.04% vs. 1.00%; $p = 0.014$) and diabetic (2.71% vs. 0.21%; $p < 0.0001$) patients. We constructed a third multivariate model (model #3) in which we analyzed the interaction between MS and diabetes with adjustment for other covariates. In this model, the risk of mortality was increased by 2.69-fold (95% CI 1.43 to 5.06; $p = 0.002$) in

Table 3 Univariate Analysis of Potential Risk Factors for Operative Mortality

Risk Factors	Age-Adjusted Relative Risk	95% CI	p Value
Age >75 yrs	3.40	2.16–5.37	<0.0001
Female gender	1.97	1.25–3.11	0.003
Metabolic syndrome (NCEP-ATPIII)	2.77	1.72–4.45	<0.0001
Active smoker	1.11	0.60–2.04	0.75
Diabetes mellitus	1.49	0.96–2.33	0.078
BMI			
Normal weight (BMI 18.5–24.9)	1.00	Referent	—
Underweight (BMI <18.5)	10.28	3.83–27.63	<0.0001
Overweight (BMI 25.0–29.9)	0.89	0.51–1.55	0.68
Obese (BMI ≥30.0)	1.10	0.61–2.00	0.75
Microalbuminuria ≥20 mg/l	1.55	0.59–4.04	0.37
Functional CCS class IV	1.54	0.92–2.57	0.10
Peripheral vascular disease	2.32	1.44–3.75	0.0006
COPD	2.21	1.30–3.75	0.003
Renal failure	3.44	1.97–5.99	<0.0001
Left ventricular ejection fraction <40%	2.10	1.12–3.93	0.021
Left main stenosis ≥50%	1.37	0.74–2.52	0.31
NCEP-ATPIII criteria			
Waist circumference (>102 cm in men and >88 cm in women)	1.76	1.05–2.94	0.33
Fasting glycemia ≥6.1 mmol/l	1.96	1.26–3.05	0.003
Triglycerides ≥1.69 mmol/l	1.14	0.72–1.80	0.57
HDL cholesterol (<1.04 mmol/l in men and <1.29 mmol/l in women)	1.29	0.82–2.01	0.27
Hypertension	2.34	1.33–4.12	0.003
Previous cardiovascular events			
MI	1.36	0.87–2.13	0.18
MI within 7 days before surgery	4.03	1.93–8.41	0.0002
Stroke	2.82	1.46–5.42	0.002
Atrial fibrillation	1.40	0.60–3.29	0.445
Previous coronary artery dilatation/stenting	1.21	0.63–2.30	0.57
Operative variables			
Operative status			
Elective	1.00	Referent	
Urgent	2.50	1.60–3.91	<0.0001
Emergent	6.37	1.44–28.15	0.015
Mammary artery graft	0.39	0.23–0.68	0.0008
Off-pump bypass surgery	0.49	0.15–1.57	0.23
Cardiopulmonary bypass time >120 min	5.25	2.70–10.22	<0.0001

BMI = body mass index; CI = confidence interval; other abbreviations as in Tables 1 and 2.

patients with MS and diabetes and 2.36-fold (95% CI 1.26 to 4.41; p = 0.007) in patients with MS and no diabetes (Fig. 2). However, the mortality risk was not significantly increased in patients with diabetes and no MS: 0.19-fold (95% CI 0.03 to 1.4; p = 0.11).

To further corroborate the results of the multivariate logistic regression models presented earlier, we performed a propensity score analysis. The propensity score was calculated to adjust for covariate differences between MS and no MS groups. After adjusting for the propensity score, age, body mass index, emergent/urgent operation, previous stroke, peripheral vascular disease, and renal failure, MS remained a strong independent predictor of operative mortality: RR 2.98 (95% CI 1.72 to 5.16; p = 0.0001). The RR 2.53 (95% CI 1.44 to 4.44; p = 0.0012) was also similar when using a conditional logistic model with propensity-based matching cohort.

Table 5 presents the causes of death. The most common cause of death was cardiac in 57.3% of the cases. There was no significant difference between MS and non-MS patients with regard to the distribution of cause of death. There were more postoperative stroke (2.3% vs. 1.4%; p = 0.014), renal failure (12.4% vs. 6.8%; p < 0.0001), and infectious complications in patients with MS than in those without MS (Table 6). Among infectious complications, patients with MS had more pneumonia (2.0% vs. 1.2%; p = 0.017) and mediastinitis (2.0% vs. 0.7%; p < 0.0001). After adjustment with the propensity score and other covariates, MS remained independently associated with the following postoperative complications: stroke, RR 1.61 (95% CI 1.03 to 2.53; p = 0.037);

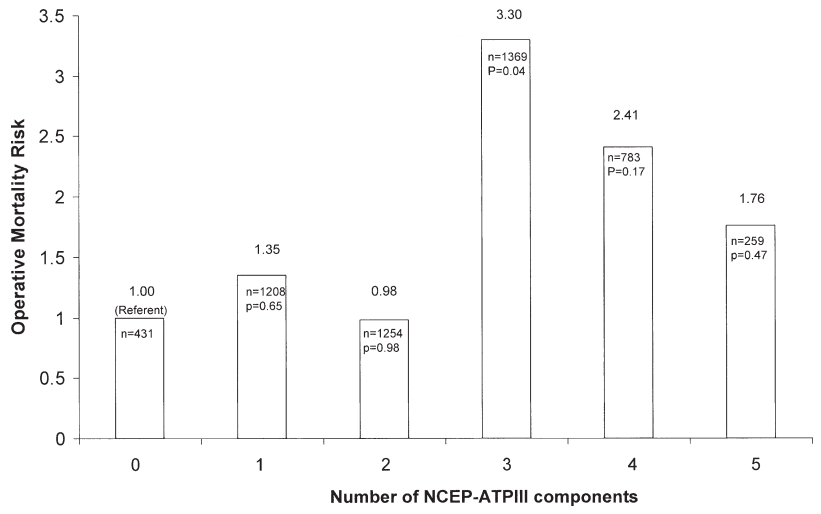

Figure 1 The Effect of the Number of Metabolic Syndrome Components on Operative Mortality Risk

The operative mortality risk was adjusted for age and gender, and the group with no component of the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) was used as the referent.

renal failure, RR 2.20 (95% CI 1.75 to 2.78; $p < 0.0001$); mediastinitis, RR 2.93 (95% CI 1.60 to 5.37; $p = 0.0003$); and pneumonia, RR 1.79 (95 CI 1.09 to 2.95; $p = 0.022$). The incidence of perioperative MIs was similar in both groups. In addition, the magnitude of myocardial tissue damage as measured with the maximum postoperative rise of CK-MB was similar in both groups (41 ± 78 μg/ml in MS patients vs. 41 ± 68 μg/ml in non-MS patients [$p = 0.91$]). Moreover, there was no significant difference between groups with regard to the maximum postoperative rise of troponin I that was measured in 4,573 patients of the cohort (MS: 31 ± 65 μg/l vs. no MS: 31 ± 66 μg/l [$p = 0.75$]).

Discussion

The most important contribution of this study was to demonstrate that MS is a strong and independent predictor of operative morbidity and mortality after a CABG surgery. These findings have major clinical implications given that: 1) MS was found to be highly prevalent in our population of patients submitted to a surgical revascularization; and 2) MS is a potentially preventable or modifiable risk factor. In the general population, MS has been reported to reach up to 25% of the population, whereas in our study 46% of the patients undergoing CABG had MS. This finding is consistent with previous studies showing a similar prev-

Table 4 Multivariable-Adjusted Relative Risk of Operative Mortality

Risk Factors	Relative Risk	95% CI	p Value
Age >75 yrs	2.72	1.64–4.50	0.0001
Female gender	1.59	0.96–2.62	0.070
Metabolic syndrome (NCEP-ATPIII)	3.04	1.73–5.32	0.0001
Body mass index			
Normal weight	1.00	Referent	—
Underweight	11.07	3.60–34.01	<0.0001
Overweight	0.71	0.39–1.28	0.26
Obese	1.55	0.80–3.00	0.19
Previous stroke	2.01	0.98–4.15	0.058
Peripheral vascular disease	1.66	0.97–2.84	0.064
Renal failure	2.44	1.30–4.55	0.005
Operative status			
Elective	1.00	Referent	—
Urgent	2.18	1.36–3.49	0.001
Emergent	5.54	1.18–26.11	0.03
Cardiopulmonary bypass time >120 min	5.65	2.82–11.33	<0.0001

CI = confidence interval; NCEP-ATPIII = National Cholesterol Education Program–Adult Treatment Panel III.

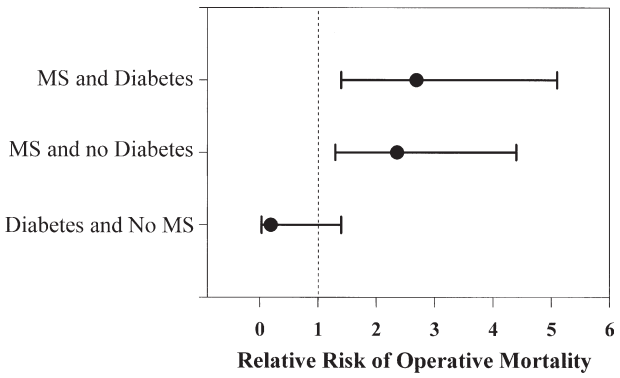

Figure 2 Adjusted Relative Risk for Operative Mortality According to MS and Diabetes

The relative risk was adjusted for age and other covariates, and the group with no metabolic syndrome (MS) and no diabetes was used as the referent. The **error bars** represent the 95% confidence interval.

alence of MS among patients with coronary artery disease (CAD) (17).

Comparison with previous studies. Whereas diabetes and obesity have been associated with increased adverse perioperative events after a CABG, previous studies have not attempted to delineate the role of MS on the operative mortality. Obesity or diabetes have been investigated in multiple studies and have been generally associated with an increased operative morbidity (2,3). Although some studies have documented an increased operative mortality after CABG in diabetic patients, others have not found such an excess mortality rate in this population (3–5). As opposed to MS, diabetes or obesity per se were not found to be independent predictors of operative mortality in our study. Diabetic patients with MS had a markedly increased risk of operative mortality, whereas those without MS were not at higher risk. The effect of MS has not been taken into account in previous studies (3–9), which might, at least in part, explain the conflicting results obtained with regard to

Table 5 Perioperative Cause of Mortality for Patients Undergoing CABG According to Metabolic Syndrome Status

		Metabolic Syndrome		
Cause	All Patients	Absent	Present	p Value
Cardiac	47 (57.3%)	13 (52.0%)	34 (59.6%)	0.52
Neurologic	11 (13.4%)	5 (20.0%)	6 (10.5%)	0.14
Septicemia	6 (7.3%)	2 (8.0%)	4 (7.0%)	0.34
Respiratory	6 (7.3%)	2 (8.0%)	4 (7.0%)	0.34
Multiple system failure	4 (4.9%)	—	4 (7.0%)	—
Renal	1 (1.2%)	—	1 (1.8%)	—
Vascular	1 (1.2%)	—	1 (1.8%)	—
Others	5 (7.3%)	2 (12.0%)	3 (5.3%)	0.32
Total	82 (100.0%)	25 (30.5%)	57 (69.5%)	<0.0001

CABG = coronary artery bypass grafting.

Table 6 Perioperative Complications After CABG

	Metabolic Syndrome		
Complications	Absent	Present	p Value
Perioperative MI	15.5%	16.3%	0.44
Stroke	1.4%	2.3%	0.014
Renal failure	6.8%	12.4%	<0.0001
Pneumonia	1.2%	2.0%	0.017
Mediastinitis	0.7%	2.0%	<0.0001
Septicemia	0.5%	0.8%	0.17

CABG = coronary artery bypass grafting; MI = myocardial infarction.

the association between diabetes and operative mortality. The results of the present study suggest that the metabolic abnormalities associated with MS have a much greater impact on short-term outcome after CABG than isolated diabetes does. These results are also consistent with a previous report indicating that the prevalence of CAD is relatively low in diabetic patients without MS whereas it is markedly increased among diabetic patients with MS, suggesting that the metabolic perturbations associated with MS are key factors in the development of atherosclerosis and cardiovascular events (18).

The causes of death among patients with or without MS were similar and were predominantly of cardiac origin followed by neurologic causes, which is in agreement with a previous study (3). We found similar incidence of infectious-related death among patients with MS versus those without MS, as opposed to what has been reported in diabetic patients (3). Nonetheless, MS patients had an increased incidence of infectious complications after CABG surgery. In addition, MS was independently associated with an increased risk of postoperative stroke and renal failure. However, the incidence of perioperative MIs was similar between the patients with or without MS.

Potential mechanisms responsible for the association between MS and operative mortality after CABG. The MS is characterized by a low-grade inflammatory state accompanied by increased circulating levels of inflammatory cytokines (19). Different mechanisms contribute to this pro-inflammatory state. Visceral adipocytes have been shown to produce more interleukin-6 than their subcutaneous counterparts, which in turn stimulates liver production of C-reactive protein (20). Furthermore, increased circulating level of tumor necrosis factor-alpha has been documented in patients with MS (21). In addition, fat specific proteins, or adipokines, are modulated by obesity. Patients with MS have reduced plasma adiponectin concentrations, whereas leptin and resistin levels are elevated (22). As opposed to leptin and resistin, which activate the immune system, adiponectin inhibits the inflammatory activation of the vascular wall largely through the inhibition of the nuclear factor kappa B pathway (23). Therefore, the pro-inflammatory state associated with MS might contribute to exacerbate the systemic inflammatory response to cardiopul-

monary bypass and surgical trauma and thus predispose to the occurrence of related perioperative complications (24).

In addition to the production of numerous proteins with immunomodulatory activity, adipocytes also produce the pro-thrombotic plasminogen activator inhibitor (PAI)-1, which is elevated in obese subjects (25). Hence, a pro-thrombotic state, which is a frequent occurrence in the postoperative period of CABG, might be exacerbated in patients with MS, thus explaining the increased incidence of thrombo-embolic events in this population. In a midterm follow-up study, Yilmaz et al. (26) have reported that MS is a predictor of saphenous vein grafts occlusion after CABG. In the present study, we have not detected an increased incidence of perioperative MI or myocardial tissue damage in MS patients. However, perioperative MI is likely not determined by early graft occlusion but rather by factors related to myocardial protection strategies or unknown factors, which could explain the absence of difference between patients with or without MS. Other factors, such as an abnormal vasoactive response, might contribute in the postoperative period to hemodynamic instability. Indeed, insulin-resistant subjects are characterized by an altered endothelial-dependent vasodilation (27). Therefore, although speculative for the moment, loss of vasodilation, increased vasospastic stimuli, and a pro-thrombotic state might all contribute to hemodynamic instability during the early postoperative period, which could contribute to the worse outcome observed in patients with MS.

Clinical implications. We found that MS is a highly prevalent and powerful risk factor for operative mortality after CABG surgery, a finding that has major clinical implications. For instance, MS is a potentially preventable and modifiable condition that often goes undiagnosed and untreated. Given that: 1) a large number (approximately 800,000) of CABG procedures are performed each year worldwide (5); 2) this procedure is associated with substantial operative mortality (1% to 5%) (5,28); and 3) MS is highly prevalent (40% to 50%) in this population and is associated with a 3-fold increase in mortality, it can be estimated that a considerable number of deaths occurring during the perioperative period of CABG are directly related to MS. The identification of MS could thus be useful to identify high-risk patients who would, otherwise, not be detected with the use of traditional risk factors. Hence, the integration of MS into the operative risk algorithms might contribute to improve risk stratification.

Considering that patients with CAD have a significant lifetime risk to develop complications requiring CABG surgery, secondary prevention in these patients could contribute to markedly reduce the operative mortality associated with MS. In light of the results of this study, aggressive treatment of the components of MS should be considered in patients with known CAD not only to decrease the overall risk of acute coronary events but also to reduce the operative risk in the event a CABG surgery is required in these patients. In this regard, it should be pointed out that many of the components of MS are not reversed by the pharmacological treatment of traditional risk factors. Indeed, the pharmacological agents (i.e., statins, angiotensin-converting enzyme inhibitors, beta-blockers) that are most often used in patients with CAD have no or little effect on the metabolic perturbations associated with MS. Furthermore, such approaches fail to target a central factor in the etiology of the prevalent form of MS (i.e., visceral obesity). Thus, the treatment of the components of MS requires aggressive changes in lifestyle habits such as increasing physical activity and implementing dietary changes leading to weight reduction and loss of visceral fat (29). In addition to lifestyle modifications, newer pharmacologic approaches (30) that specifically target some of the key causal mechanisms of MS might also be considered as becoming part of the secondary prevention strategy in patients with CAD. Secondary prevention should also become an important consideration in patients with MS who already underwent CABG, given that these patients are at risk for graft occlusion (26) and thus re-operation. The aggressive treatment of MS with the use of behavioral or pharmacological approaches might thus contribute to substantially reduce operative morbidity and mortality in these patients at the time of re-operation.

In contrast, it remains to be determined whether it is possible to acutely modify some of the components of MS in the pre- and/or perioperative period in patients planned for CABG surgery and whether these modifications are able to significantly reduce operative risk associated with MS. In particular, it would seem difficult to modify the central component of MS (i.e., the visceral adiposity) within a very short period of time. Nonetheless, it is possible that some of the metabolic perturbations linked to visceral obesity might be modifiable in the short term. To this effect, it has recently been demonstrated that a tight control of perioperative glycemia might improve operative outcomes in patients with diabetes (31). Further studies are necessary to determine whether perioperative glycemia control (31) or other acute pharmacological interventions might be successful to reduce operative risk in MS patients planned for CABG surgery (30,32). Further prospective studies are needed to understand the key mechanisms that are responsible for the increased operative mortality after CABG in patients with MS. This new knowledge could pave the way to new pharmacologic therapy able to acutely modify the operative risk associated with MS.

Study limitations. The study was retrospective in nature. However, all the data including the complications were prospectively collected by trained personnel. Major postoperative adverse events were also prospectively validated by an experienced cardiac surgeon according to standard definitions. Several crucial plasma metabolic markers (e.g., insulinemia, inflammatory markers, PAI-1) were not measured in this study. It was thus not possible to investigate the potential mechanisms responsible for the significant and independent association between MS and operative mortality. Patients with MS had more comorbidity. Consistently,

their operative risk assessed with the Parsonnet score was higher, confirming the fact that this population is at higher operative risk. One could thus argue that confounding variables might have contributed to the association observed between MS and mortality. However, when adjusting for all the reported risk factors associated with poor outcome after CABG, MS remained a strong and independent predictor for operative mortality. In addition, propensity analysis has been used to reduce the effect of potential confounding variables, and the result of this analysis has confirmed the strong and independent association of MS with operative mortality. These results therefore support the usefulness of the identification of MS for operative risk stratification before CABG surgery.

Conclusions

This is the first study to report that MS is a strong and independent risk factor for operative mortality after CABG surgery. Given that MS is a frequent and modifiable risk factor, the elaboration of prospective strategies focusing on the aggressive treatment of its components could possibly contribute to reduce operative mortality in patients undergoing surgical coronary revascularization. Additional studies are warranted: 1) to elucidate the mechanisms that are responsible for the association between MS and CABG operative mortality; and 2) to identify the components of MS that should be considered as new therapeutic targets in patients with CAD and especially those who are planned for CABG.

Acknowledgments

The authors would like to thank Martine Fleury, Brigitte Dionne, and Stéphanie Dionne for their technical assistance.

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